Dietary Boron: Progress in Establishing Essential Roles in Human and Animal Physiology

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ABSTRACT: This review summarizes the progress made in establishing essential roles for boron in human and animal physiology and assesses that progress in view of criteria for essentiality of elements. The evidence to date suggests that humans and at least some higher animals may use boron to support normal biological functions. These include roles in calcium metabolism, bone growth and maintenance, insulin metabolism, and completion of the life cycle. The biochemical mechanisms responsible for these effects are poorly understood. However, the nature of boron biochemistry suggests specific lines of investigation. In particular, further characterization of the cell signalling molecules capable of complexing with boron should provide insights into the specific biochemical function(s) of boron in humans.

1 INTRODUCTION

Boron has long been recognized as essential for all higher plants in phylogenetic kingdom Viridiplantae (Warington, 1926). More recently, boron was recognized as required for at least some organisms in Eubacteria (Chen et al., 1981), Stramenopila (Lovatt, 1985), and Animalia (Fort et al., 2002; Rowe, 1999). Specific species in the Fungi kingdom have a demonstrated physiological response to boron, an important finding because Fungi species are thought to share a common ancestor with animals exclusive of plants (Carney et al., 2004). This review summarizes the progress made in establishing essential roles for boron in human and animal physiology and assesses that progress in relation to accepted criteria for essentiality of elements (Expert Consultation WHO/FAO/IAEA, 1996; Frieden, 1984; Mertz, 1970; Underwood et al., 1987). Those criteria are: 1) it reacts with biological material or forms chelates; 2) it is present in healthy tissues of different animals at comparable concentrations; 3) toxicity results only at relatively high intakes; 4) tissue concentrations during short term variations in intake are maintained by homeostatic mechanisms; 5) depletion prevents growth and completion of the life cycle; 6) depletion consistently results in reduction of a physiologically important function; and 7) when an integral part of an organic structure, depletion causes reduction in performance of a vital function.

2 BORON BIOMOLECULES

2.1 *Boron chemistry*

Organoboron compounds are those organic compounds that contain B-O bonds, i.e., the orthoborates $(B(OR)_3$, $(RO)B(OR')_2$ and $(RO)B(OR')(OR'')$, and orthoborates of polyhydric alcohols (Greenwood et al., 1984). Organoboron compounds also include B-N compounds, because B-N is isoelectronic with C-C (Greenwood, 1973). Organoboron compounds are apparently important in biological systems and they are the result of interaction with OH or amine groups. As described below, organoboron complexes occur in plants and are produced in vitro with biomolecules isolated from animal tissues.

The most probable form of dietary boron after ingestion and subsequent hydrolysis (Greenwood, et al., 1984) is orthoboric acid (common name: boric acid) $B(OH)_3$. Boric acid accepts a hydroxyl ion (a Lewis acid) to form the tetrahedral anion $B(OH)_4^-$ (Reaction 1) (Greenwood, 1973):

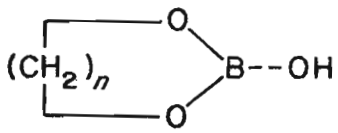
$$B(OH)_3 + 2H_2O \leftrightarrow H_3O^+ + B(OH)_4^- \quad pK_a = 9.25\ (25°C) \quad (1)$$

At typical physiological boron concentrations (0.006 - ~9.0 μmol/L) in plants, animals, or humans, inorganic boron is essentially present only as the mononuclear species boric acid $B(OH)_3$ and as borate $B(OH)_4^-$ (Weser, 1967). Within the normal pH range of the gut and kidney, $B(OH)_3$ prevails as the dominant species (pH 1: ~100% B(OH)3; pH 9.3: 50%; pH 11: ~0%) (Spivack et al., 1987).

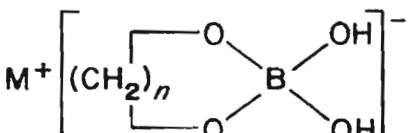
2.2 Boron biochemistry

2.2.1 Boron esters

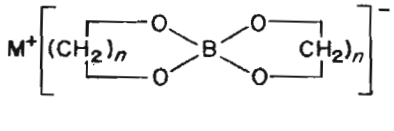
There is a vast number of mono or polyhydroxy compounds that contain one or more hydroxy groups with suitable positions for interaction with boron to form boroesters, specific organoboron complexes. For example, boric acid reacts with a suitable dihydroxy compound to form the corresponding boric acid monoester ("partial" esterification) (e.g., Structure 1) that retains the trigonal-planar configuration and no charge. Borate may react with a suitable dihydroxy compound to form the corresponding borate monoester ("partial" esterification; monocyclic) (Structure 2) with a tetrahedral configuration and a negative charge. A compound of similar configuration and charge is also formed when a boric acid monoester forms a complex with an available hydroxyl group. These two types of boromonoesters can react with another dihydroxy compound to give a corresponding spiro-cyclic borodiester ("complete" esterification) that is a chelate complex with a tetrahedral configuration and negative charge (Structure 3) (Van Duin et al., 1984).



(Structure 1)



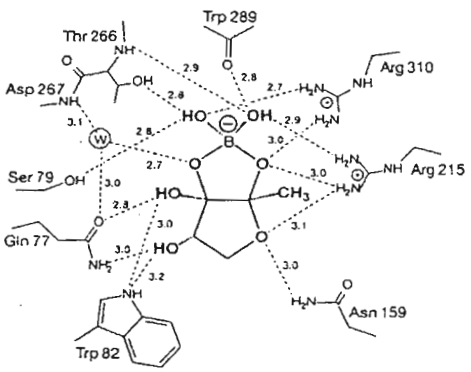
(Structure 2)



(Structure 3)

2.2.2 Boron-Containing Biomolecules

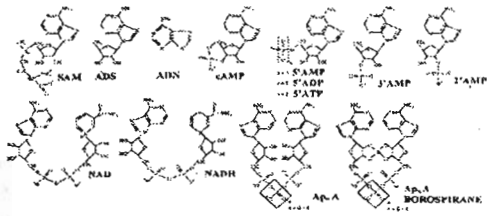
Since discovery of the first boron biomolecule in 1967 (Hutter et al., 1967), several other similar biomolecules are now well-characterized (Loomis et al., 1992; O'Neill et al., 1996; Schummer et al., 1994). Most recently described was a cell-to-cell communication signal that requires boron (Chen et al., 2002). This cell signalling biomolecule, autoinducer-II (AI-II), is produced by a bacterium and binds to the primary receptor to form a furanosyl borate diester complex (Structure 4).



(Structure 4)

The discovery of all currently recognized boron-dependent biomolecules was achieved because the bound boron formed four coordinate covalent bonds with the ligand, creating a thermodynamically stable complex that is almost undissociable in water (Gerrard, 1961; Thellier et al., 1979).

Ribose derivatives have a strong affinity for boron (Loomis, et al., 1992) and nucleotide-boron adduction has been demonstrated for a number of ribose-containing nucleotides and cofactors, all with different affinities for boron (Structure 5) (Ralston et al., 2001). S-adenosylmethionine (SAM), the predominant methyl donor in biological methylations and a versatile cofactor in a variety of physiological processes, has the highest known affinity for boron of all animal and human biocompounds examined (Ralston, et al., 2001). Next in rank are members of the diadenosine phosphate (Ap_nA) family of biomolecules Ap_3A, Ap_4A, Ap_5A, and Ap_6A, signal nucleotides present in all cells with active protein synthesis (McLennan, 1992).



(Structure 5)

The physiological consequences of boron binding with SAM or the Ap_nA molecular species remain unexplored but probably are not trivial. NAD^+ (Structure 5) follows Ap_3A in rank for boron affinity (Ralston, et al., 2001) and oxidoreductase enzymes that require pyridine (e.g., NAD^+ or NADP) or flavin (e.g., FAD) nucleotides are well known to be competitively inhibited by borate or its derivatives (Kim et al., 2003; Smith et al., 1976). Reversible enzymatic inhibition as an essential role for an element is unusual. However, there is irrefutable evidence that boron serves to inhibit or dampen several metabolic pathways in plants (Lovatt et al., 1984; Shkol'nik et al., 1975).

Based on the structure of known boron-containing biomolecules, this author predicts that several biomolecules waiting discovery are derived from ribose and serve as signaling molecules that interact with the cell surface. Because known boron biomolecules are comprised of mirror or near-mirror halves stabilized by a single boron atom, it is predicted that undiscovered biomolecules have similar mirror construction.

3 BORON CONCENTRATIONS IN HEALTHY TISSUES

Boron is present at comparable concentrations in healthy tissues of different animals. Similar concentrations of boron (μg/mL) were reported in the plasma of humans (0.017-0.191) (Ferrando et al., 1993; Hunt et al., 1997; Iyengar et al., 1990; Mauras et al., 1986; Usuda et al., 1997; Wallace et al., 2002; Ward, 1993), rats (0.038-0.039) (Vaziri et al., 2001), chicks (0.047-0.152) (Hunt, 1996), cows (0.052-0.153) (Small et al., 1997), lambs (0.163) (Hunt, 1996), pigs (0.126) (Hunt, 1996), and horses (0.227) (Hunt, 1996). Liver boron concentrations (μg/g; dry weight) are similar in humans (1.1-5.4) (Shuler et al., 1990; Ward, 1987), rats (0.51) (Bai et al., 1996), chicks (1.01-4.4) (Rossi et al., 1993), and cows (3.3) (Ward, 1987); for brain tissue (μg/g; dry weight), similar in humans (0.87) (Shuler, et al., 1990), rats (0.64) (Bai, et al., 1996), and chicks (1.01-1.05); for bone tissue (μg/g; dry weight), similar in humans (1.6) (Ward, 1993), rats (1.3) (Bai, et al., 1996), chicks (0.59-0.64) (Wilson et al., 1996), and mule deer (1.7) (Stelter, 1980).

4 ENVIRONMENTAL BORON

4.1 *Dietary intakes of boron*

Boron is ubiquitous in the environment and, on a molar basis, adult Americans consume more boron than several essential trace elements, e.g., copper, manganese, and molybdenum (Hunt et al., 2001). Boron consumption varies considerably among individuals and by sex-age group. For example, boron intake for infants aged 0 to 6 months is 0.75±0.14 mg/d (mean±SE) (1^{st} percentile, 0.03; 99^{th} percentile, 6.40 mg/d); for males aged 51 to 70 years, 1.34±0.02 mg/d (1^{st} percentile, 0.39; 99^{th} percentile, 3.34 mg/d); for lactating females, 1.39±0.16 mg/d (1^{st} percentile, 0.38; 99^{th} percentile, 3.49 mg/d) (Food and Nutrition Board: Institute of Medicine, 2001). The range of dietary boron intakes within a sex-age group arises from a variety of factors. For example, compared with animal-based food products, plant-based products are much richer sources of dietary boron (Hunt, et al., 2001). Furthermore, most plant species within the subclass *Dicotyledoneae*, which includes fruits [i.e., raw pears: 2.27 μg (0.21 *μmol*) B/g], vegetables, tubers and legumes have much higher concentrations of boron than do species from the subclass *Monocotyledoneae*, especially gramineaceous species (the grasses) including rice [0.09 μg (0.008 *μmol*) B/g], corn, barley, and wheat (Hunt, et al., 2001). For this reason, there are many diets otherwise nutritionally adequate that provide only 0.36 mg B/2000 kcal and are prepared easily by excluding vegetables, tubers, nuts, and legumes (Hunt, et al., 1997).

4.2 *Boron toxicity*

Boron has a range of safe exposures and it produces toxicity in all tested biological organisms when excessive amounts are absorbed. Boron dose response experiments to determine embryo-larval malformations in the frog *X. laevis* have demonstrated the pattern of areas of survival, deficiency, optimization, toxicity, and lethality that are characteristic of an essential element (Fort, et al., 2002).

Gastrointestinal absorption of boron approaches 100% (Hunt, et al., 1997). Even so, boron has a low order of toxicity. For adults, the Tolerable Upper Intake Level (UL) for boron is 20 mg/d (Food and Nutrition Board: Institute of Medicine, 2001), i.e., 20-fold typical intakes. Potentially lethal doses are generally cited as 3 g (3,000 mg) to 6 g (6,000 mg/) for infants and 15 g (15,000 mg) to 20 g (20,000 mg) of boric acid for adults (Litovitz et al., 1988). At pre-

sent, death from boron poisoning is exceptionally rare probably because of the emphasis placed on maintaining electrolytic balance and supporting kidney function during the worst part of the poisoning incident.

5 BORON HOMEOSTATIC MECHANISMS

5.1 Boron gradient concentrations

There are several lines of evidence that suggest that boron may be regulated in humans. That boron contents in human milks were similar and stable throughout lactation of full term infants in two cohorts of women living in either Houston, TX, (Hunt et al., 2005) or St. John's, Newfoundland (Figure 1) (Hunt et al., 2004) has been interpreted as suggestive of regulatory mechanisms for the element, which remain undefined.

Substantial increases in dietary boron in elderly women [0.3 mg/d (1st percentile of typical intake) to 3.0 mg/d (~99th percentile of typical intake)] resulted in only small changes in blood boron values (Hunt, et al., 1997). Other investigators have also reported a remarkably narrow range of boron concentrations in whole blood from subjects with unknown dietary histories (Clarke et al., 1987).

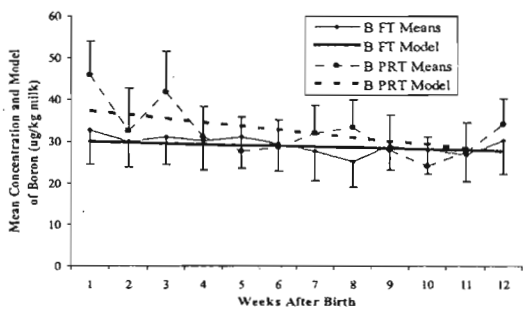


Figure 1. Model and mean (±SE) concentrations of boron in breast milk from mothers of full-term (FT) and premature (PRT) infants; n = 9 per group over the 12 wk after birth. During the first 12 wk of lactation, prematurity affected the rate of change in concentrations (P = 0.01).

Work with higher mammals also suggests that boron may be regulated. In female rats, supplementation with high amounts of boron (9.25 mmol/L water) for 21 days, caused an increase in plasma boron concentrations but an undefined homeostatic mechanism concurrently eliminated any excess of boron from the liver and brain against their own concentration gradients (Magour et al., 1982). In yearling beef heifers, the percent of filtered boron reabsorbed by the kidneys decreased significantly with increased boron intake (Green et al., 1977). In general, the findings to present suggest the presence of boron concentration against a gradient across mammalian cell membranes.

5.2 Boron transporters

The recent report (Ralston et al., 2004) that cultures of either RAW 264.7 cells or HL60 cells retain intracellular boron against a concentration gradient indicated the presence of intracellular boron binding species or the existence of boron specific transporters on the plasma membrane. Most likely, the repeated demonstration of the concentration of boron against a gradient indicates the existence of boron specific transporters. This line of evidence for the homeostatic control of boron is enhanced further by the discovery of a specific mammalian borate transporter, NaBC1, expressed in the basolateral membranes of epithelial cells (Park et al., 2004). The recent identification of the boron transporter, BOR1 (AtBor1), in the flowering plant *Arabidopsis thaliana* (Takano et al., 2005; Takano et al., 2002) and its mammalian homolog, BTR1, a newly discovered bicarbonate transporter superfamily member (Parker et al., 2001), provides further evidence for the homeostatic control of boron in humans and mammals.

6 BORON DEPLETION AND THE LIFE CYCLE

There are several lines of evidence that suggest that boron depletion prevents growth and completion of the life cycle in animal models. The original finding (Hunt et al., 1981) that boron deprivation can impair growth has been the basis for further research in several independent laboratories. Boron depletion can prevent growth and completion of the life cycle in the zebrafish. For example, in experiments with zebrafish, sperm from low-boron males successfully fertilized eggs from low-boron females (Rowe et al., 1999), but 92% of the embryos (compared to 37% of controls) died within 10 days. However, the low-boron embryos could be rescued from death if repleted with boron during the first hour after fertilization. Studies with the South African clawed frog, *Xenopus laevis* (Fort, et al., 2002), indicate that specimens fed a low-boron diet in a low-boron culture media produced a substantially higher number of necrotic eggs and fertilized embryos than frogs fed a boron-sufficient diet. By 96 hours of development, none of the larvae from boron-deficient adults maintained in low-boron culture media developed normally. Similar findings were reported for rats in which a low-boron diet (0.04 μg/g) reduced the number of implantation sites compared to a diet supplemented with boron (Lanoue et al., 1998).

7 BORON DEPLETION AND PHYSIOLOGICAL/STRUCTURAL ABNORMALITIES

One of the criteria of essentiality, as defined by WHO, is a reduction in a physiologically important function when reduction in element exposure falls below a certain limit (Expert Consultation WHO/FAO/IAEA, 1996). Several lines of evidence indicate the boron deprivation appears to perturb physiological processes in frogs, zebrafish, chicks, rats, pigs, and humans.

7.1 Boron and calcium metabolism and bone growth and maintenance

Observations in human studies suggest that boron can influence calcium metabolism. For example, an increase in boron intake (0.36 to 3.23 mg/d) by postmenopausal women resulted in a 5% increase in urinary calcium excretion (Hunt, et al., 1997). Because increases in dietary calcium often result in increased urinary calcium excretion, this finding may reflect an increase in intestinal calcium absorption. Thus, it is important to determine whether the primary effect of boron on calcium metabolism is at the level of enteric absorption.

Bone calcification and metabolism respond to boron nutrition. Maturation of the growth plate was retarded during dietary boron deprivation in the chick (Hunt et al., 1994). Boron deprivation reduced bone strength in pigs (Armstrong et al., 2000) and rats (Nielsen, 2004) and induced abnormal limb development in frogs (Fort et al., 2000). In other studies, a boron supplement increased bone strength in nutritionally adequate chicks (Wilson et al., 1998) and adult rats (Chapin et al., 1998).

There is considerable evidence that dietary boron alleviates the signs of marginal vitamin D deficiency. Marginal vitamin D deficiency elevates plasma alkaline phosphatase concentrations, reduces body weight, and impairs bone structure. In the growing rachitic chick, dietary boron reduced elevated serum concentrations of alkaline phosphatase (Hunt, et al., 1981; Kurtoglu et al., 2001), improved body weight (Bai et al., 1996; Kurtoglu, et al., 2001), and substantially alleviated the perturbed histomorphometric indices of bone growth cartilage (Hunt, 1989; Hunt, et al., 1994).

7.2 Dietary boron and insulin metabolism

Pancreatic β-cells easily induced to secrete mass quantities of insulin are readily damaged, which eventually can cause them to stop functioning and result in diabetes mellitus (Reaven, 1999; Sprietsma et al., 1993). It is possible that dietary boron may reduce the amount of insulin needed to maintain glucose levels, thus limiting β-cell deterioration. For example, as a dietary ingredient, boron decreased peak pancreatic in situ insulin release in chicks (Figure 2). In rats, dietary boron decreased plasma insulin concentrations but did not change glucose concentrations (Bakken et al., 2003). Work is underway to determine whether dietary boron can reduce β-cell "exhaustion" and deterioration.

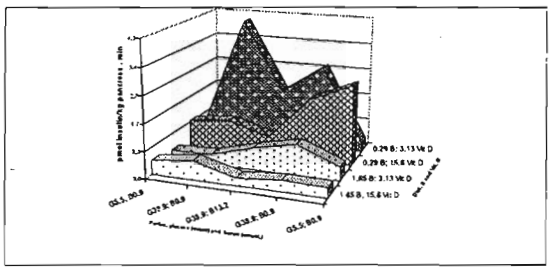


Figure 2. Alteration in peak insulin secretion from isolated, perfused pancreata from 1-d-old cockerels fed a diet containing 0.29 (boron-low) or 1.65 mg B/kg and supplemented with cholecalciferol (Vit D) at 3.13 (inadequate) or 15.60 (adequate) μg/kg for 26-37 d. Perfusion phases varied in the total amount of glucose (G: 5.5 or 38.0 mmol/L) and boron (B; 0.9 or 13.2 μmol/L) in the perfusate.

8 CONCLUSIONS

Boron is a natural constituent of the diet. Adult Americans consume slightly less than 1.0 mg per day on average and can easily increase that average by increasing consumption of fruits and vegetables. The evidence to date suggests that humans and at least some higher animals may use boron to support normal biological functions. The biochemical mechanisms responsible for these effects are poorly understood. However, the nature of boron biochemistry suggests specific lines of investigation. In particular, further characterization of the cell signalling molecules capable of complexing with boron should provide insights into the specific biochemical function(s) of boron in humans.

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III. ULUSLARARASI
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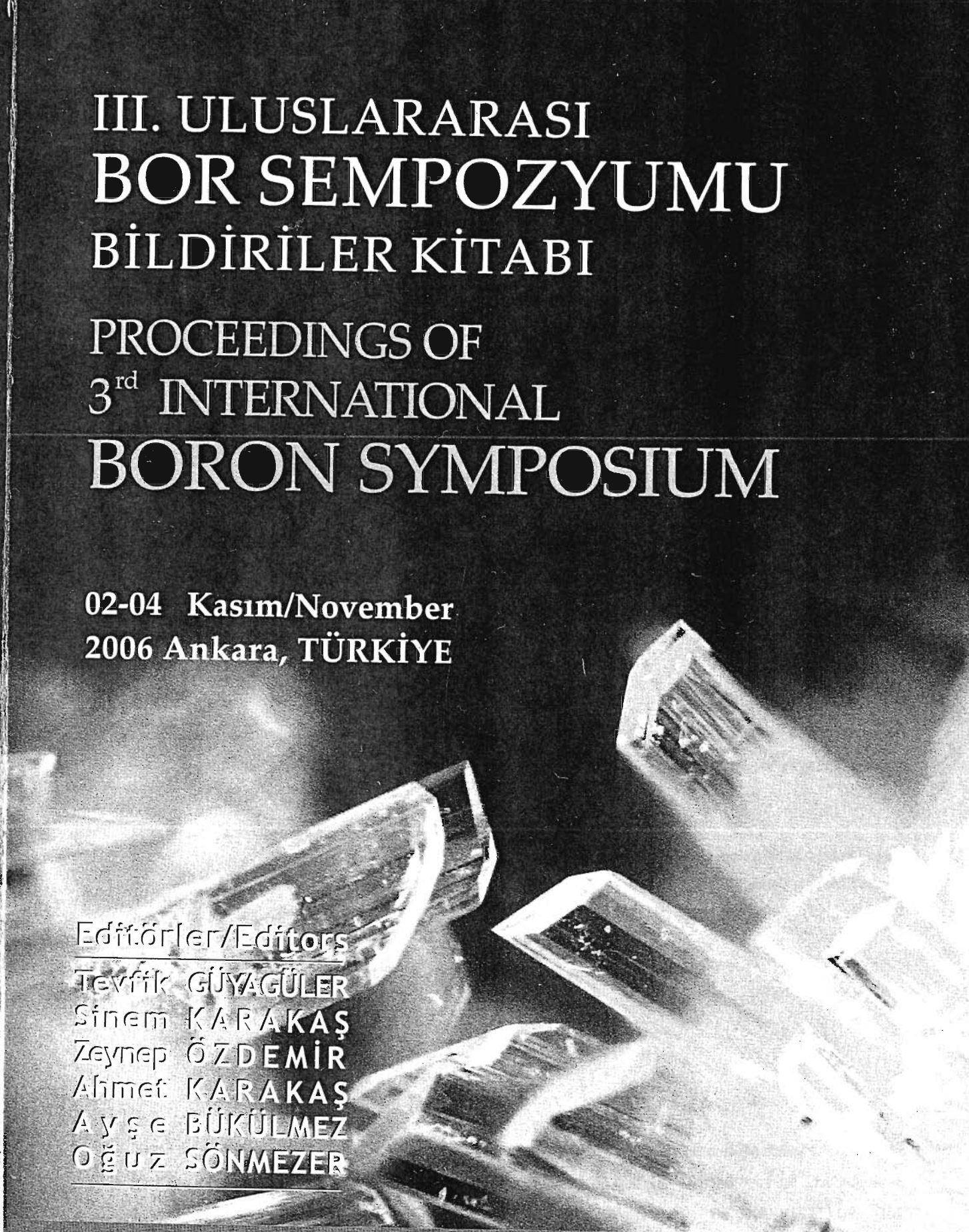

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